PHARMACEUTICAL COMPOSITION TO CONTROL BLOOD GLUCOSE IN PATIENTS WITH TYPE 2 DIABETES

FIELD OF THE INVENTION

This invention consists of providing a therapeutic combination consisting of Sulfonylurea Glymepirid and Biguanide Metformin, both oral hypoglycemics, which, when combined, produce an additive effect and therefore greater effectiveness in controlling blood glucose levels in patients with Type 2 Diabetes.

BACKGROUND

The use of Sulfonylureas in treating type 2 diabetes is fully established as an effective means of controlling hypoglycemia. At the molecular level, Sulfonylureas act on the receptor in β pancreatic cells known as SUR, which, when it is activated, closes an ATP dependent potassium channel, which in turn causes a reduction in potassium intake and in consequence depolarization of the membrane. This in turn causes an increase in the flow of calcium toward the cell's interior, activating the cytoskeleton, which causes translocation of secretory granules, thereby releasing insulin by exocytosis.

Another treatment whose use has spread recently is with Biguanide Metformin, which acts effectively not only to control hypoglycemia but also in its prevention. Metformin has a different mechanism of action from Sulfonylureas, increasing insulin sensitivity in hepatic and peripheral tissue (mainly muscular tissues). Metformin inhibits gluconeogenesis and hepatic glycogenolisis. At the cellular level, heightened insulin sensitivity is explained by the increased activity it induces in the tyrosin cinase post-receptor and the resulting increase in the number and activity of GLUT4 transporters.

However, around 75% of type 2 diabetes patients treated with Sulfonylureas do not succeed in bringing their glucose level to the desire values, and need to complement their treatment with a second oral agent. Also, most patients with single drug treatment using Sulfonylureas after a certain number of years require an additional drug that contributes to

their control therapy in order to achieve a suitable level of glycemic control. This loss of effectiveness is attributed to various causes, which are not yet well established, such as the supposition that gradual deterioration of the pancreas renders it unable to maintain an exacerbated insulin excretion rate for a long period of time due to constant, long-term stimulation caused by Sulfonylurea therapy. However, contrary to this explanation, Metformin therapy, which does not act by over stimulating β cells, also presents lack of response after prolonged use, which would be contradictory to the explanation given for the lack of response of Sulfonylureas.

On the other hand it has been found that combining Sulfonylurea and Metformin therapy is more effective than monotherapy with either of the two medications. Thus, it has been fully proven that the hypoglycemic action of Metformin is completely additional to that of Sulfonylureas (de Fronzo, RA, Goodman AM Yn, England J. Med. 333,541 (1995))

Its also has been reported that when monotherapy with Sulfonylureas does not achieve the desired level, it should not be discontinued and replaced by Metformin monotherapy, as this will not lower glucose levels in plasma below the values observed with Sulfonylurea monotherapy (Rosenstock J, Samols E, Muchmore D B, Sheneider J. Diabetes Care 19, 1994 (1996); Gasber AJ, Duncan TG, Goodman AM, Mills DJ, Rohtf JL, Amer. J. Med. 103,491 (1997)).

It is generally recognized that, because Diabetes Mellitus is a progressive disease, patients with good initial response to oral agents will eventually require a second medication to achieve the desired glycemic control. As we have mentioned, adding Metformin to Sulfonylurea therapy or vice-versa produces an additive response, not only to the reduction in glucose, but also to the reduction in lipids (Hermann LS Schersten B, Bitzen PO, Kjellstrom T, Lindgarde F, Melander A. Diabetes Care, 17, 1100 (1994)).

DESCRIPTION OF THE INVENTION

While there are studies and antecedents for Sulfonylurea gliburide in combination with Metformin, use of Glymepirid in this combination has not been documented to date. Based on studies, we know that Sulfonylureas differ from one another in their insulin release response speed and in the degree of suppression of hepatic glucose achieved (Groop L.m, Luzzzl L, Melander A, Groop PW Rathèises K, Sinonson DC, Diabetes 36, 1320 (1987)). As we have been able to establish in this invention, this difference in response can be potentiated by combining Sulfonylureas with Metformin. It has even been reported that the combination of Metformin with a Sulfonylurea as gliburide can have a synergetic effect, given that the two agents act to improve glucose tolerance by different and complementary mechanisms. Thus, we find (Physicians Desk Reference 54th Edition, 2000, page 1349) that the combination of Metformin and gliburide acts synergically by reducing glucose in plasma between meals, glucose in post-prandial plasma and glucosylated hemoglobin to levels of –63 mg/dL –65 mg/dL and –1.7% respectively. Comparing these results with gliburide monotreatment, the net differences with the combined treatment were +13 mg/dL, -3 mg/dL and +0.2% respectively, and with Metformin monotreatment were –0.9 mg/dL-1.8 mg/dL and –0.2% respectively.

Combined Glymepirid and Metformin therapy has been suggested previously in the literature (Physicians Desk Reference, 54th Edition, 2000. Page 1349). However, no data are provided on its advantages or appropriate dosages; no clinical studies are cited, and to the contrary, they warn of its supposed risk of hypoglycemia due to concomitant use of the medication Amaryl (a trademark registered in Mexico, the USA and other countries) and Metformin. Needless to say, this bibliography does not suggest the possibility of development and use of a pharmaceutical composition with a combination of Glimpiride and Metformin, which, in this invention, we have found to offer unexpected advantages.

The purpose of this invention is to provide a pharmaceutical composition consisting of Glymepirid Sulfonylurea and Biguanid Metformin as its clorhidrate salt, and prove that oral hypoglycemic therapy combining Glymepirid and Metformin in a single

pharmaceutical form is more effective and just as safe as monotherapy with the same medications in patients with uncontrolled type 2 diabetes mellitus.

To demonstrate the above, a random, blind, double clinical study was conducted with a universe of 30 patients with uncontrolled type 2 diabetes mellitus who receive monotherapy with Sulfonylureas or Biguanides per group.

Criteria for inclusion were as follows:

1. Body mass index = 27 kg/m^2
2. Age 40 to 65
3. Capacity for deglutition
4. Voluntary consent

Criteria for exclusion were as follows:

1. Pregnancy
2. Insulin treatment
3. Personal background of systemic diseases such as:

    a) Cardiac insufficiency
    b) Hepatic or chronic hepatopathic insufficiency
    c) Renal insufficiency.

4. Background of significant chronic complications with type 2 diabetes mellitus:

    a) Renal insufficiency
    b) Ischemic cardiopathy
    c) Cerebral vascular disease
    d) Visceral neuropathy.

5. Background of short-term terminal diseases, such as:

    a) Cancer
    b) HIV

6. Therapy with medications that present pharmacological interaction with Glymepirid or Metformin, such as acetozolamide, nicotinic acid, para-aminosalicylic acid, non-steroid anti-inflammatory analgesics, hystamine antagonists 2, barbiturates, cyclofosfamide, clonidine, cloranphenicol, cumarinics, disopyramide, epinephrine, estatines, fenfluramine, phenotiacine, fibrates, fluoxetine, guanitidine, steroid hormones, ifosfamide, monoamineoxidase inhibitors, laxatives, miconazole, quinolones, reserpine, rifampicine, sulfamides, and tetracycline.

7. Known intolerance or allergies to Sulfonylureas or Biguanids.

<u>Criteria for exclusion from the therapy, but not from the statistical analysis:</u>

1. Presence of severe hypoglycemia at the maximum dosages used in the study

2. Presence of severe hypoglycemia at the minimum dosages used in the study

3. Presence of intolerable undesirable effects with any of the medications used in the study.

4. Failure to follow the medical treatment indicated.

5. Failure to attend scheduled visits.

6. Intercurrent illnesses or accidents that warrant hospitalization.

7. Administration during the study of medications with pharmacological interaction with Metformin Glymepirid.

8. Voluntary withdrawal from the study.

The variables studied were as follows:

Dependent variables:

a) Glycemia between meals
b) Glucosilated hemoglobin
c) β cell function
d) Insulin resistance
e) Metabolic profile

Independent variable:

a) Hypoglycemic therapy

Intervening variables:

a) Age
b) Sex
c) Body mass index
d) Evolution time of diabetes

Definitions:

Levels of glycemia between meals > 139 mg/dL are defined as type 2 diabetes mellitus.

Severe hypoglycemia: Glycemia between meals > 260 mg/dL

Severe hypoglycemia: Glycemia < 60 mg/dL

Non-adherence: Medication absorption <80%

Absence: Missed appointment on > 1 occasion.

Procedure:

1. Identification, clinical history and selection of participants

2. Clinical measurements and basal measurement of glycemia between meals, glucosilated hemoglobin, total cholesterol, cholesterol of high density lipoproteins, triglycerides, creatinine, uric acid, glutemic-oxaloacetic transaminase, glutemic-pyruvic transaminase, lactic dehydrogenase, alkaline and insulin fosfatase.

3. Random assignment of patients to each group and pharmacological intervention in accordance with concentration of basal glycemia:

   a) Glymepirid (2 mg tablets)

Glycemia 140-180 mg/dl	1 mg	½ tablet
Glycemia 181-220 mg/dl	2 mg	1 tablet
Glycemia 221-260 mg/dl	4 mg	2 tablets

   b) Metformin (1000 mg tablets)

Glycemia 140-180 mg/dl	500 mg	½ tablet
Glycemia 181-220 mg/dl	1000 mg	1 tablet
Glycemia 221-260 mg/dl	2000 mg	2 tablets

   c) Glymepirid/Metformin (2/1000 mg tablets)

140-180 mg/dl	1/500 mg	½ tablet

4. Clinical evaluation 30 and 60 days after beginning the study, measuring glycemia between meals and lactic dehydroginase.

5. Final clinical evaluations 90 days after the study begins, measuring glycemia between meals, glucosilated hemoglobin, total cholesterol, high density lipoprotein cholesterol, triglyceride, creatinine, uric acid, glutemic-oxaloacetic transaminase, glutemic- pyruvic transaminase, lactic dehydrogenase, alkaline and insulin fosfatase.

6. Undesirable effects were reported on a special record sheet, specifying each of the clinical manifestations considered probable, possible or directly related to the use of the drugs ingested.

The results obtained show that combined Metformin and glymeripid therapy was significantly more effective in controlling glucosilated hemoglobin levels, post-prandial blood glucose levels and blood glucose levels between meals than single-drug treatment with Glymepirid or Metformin alone. The results obtained are shown below:

	Combination	Glymepirid	Metformin
Glucosilated hemoglobin HbA_{1c}	-0.70	+0.25	+0.06
Blood glucose between meals	-1.77	+0.68	+0.75
Post-prandial blood glucose	-2.7	+0.99	+1.08

What is extraordinary about the values obtained is that monotherapy with either Glymepirid or Metformin has a similar effect in raising glucose levels, while treatment with the combination clearly shows a beneficial effect, which highlights its importance.

The previous combinations used in the clinical study can be illustrated by means of the following examples:

Example 1

A pharmaceutical composition is prepared consisting of 500 mg of Metformin Clorhidrate and 1 mg of Glymepirid, adding the following excipients:

Microcrystalline Cellulose PH 101	39.20
Coloidal Dioxide of Silica	1.80
Polividone K-90	18.00
Sodium Croscarmelose	12.00
Magnesium stereate	3.00
Clear Opadray YS-1-7006	5.00
Purified water	0.204

This pharmaceutical composition was used for the aforementioned clinical tests.

Example 2

A pharmaceutical composition is prepared consisting of 500 mg of Metformin Clorhidrate and 2 mg of Glymepirid, adding the following excipients:

Microcrystalline Cellulose PH 101	38.20
Coloidal Dioxide of Silica	1.80
Polividone K-90	18.00
Sodium Croscarmelose	12.00
Magnesium stereate	3.00
Clear Opadray YS-1-7006	5.00
Purified water	0.204

This pharmaceutical composition was used for the aforementioned clinical tests.

Example 3

A pharmaceutical composition is prepared consisting of 1000 mg of Metformin Clorhidrate and 2 mg of Glymepirid, adding the following excipients:

Microcrystalline Cellulose PH 101	78.40 mg
Coloidal Dioxide of Silica	3.60 mg
Polividone K-90	36.00 mg
Sodium Croscarmelose	24.00 mg
Magnesium stereate	6.00 mg
Clear Opadray YS-1-7006	6.25 mg
Purified water	0.345 ml

This pharmaceutical composition was used for the aforementioned clinical tests.

Example 4

A pharmaceutical composition is prepared consisting of 1000 mg of Metformin Clorhidrate and 4 mg of Glymepirid, adding the following excipients:

Microcrystalline Cellulose PH 101	76.40 mg
Coloidal Dioxide of Silica	3.60 mg
Polividone K-90	36.00 mg
Sodium Croscarmelose	24.00 mg
Magnesium stereate	6.00 mg
Clear Opadray YS-1-7006	6.25 mg
Purified water	0.345 ml

This pharmaceutical composition was used for the aforementioned clinical tests.